

## Evidence-based Practice Center Systematic Review Protocol

Project Title: Treatment of Osteoarthritis of the Knee: An Update

### I. Background and Objectives for the Systematic Review

Osteoarthritis (OA) of the knee is a condition characterized by the progressive destruction of the articular cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, accompanied by pain, immobility, and reduction in function and the ability to complete activities of daily living (ADL). Two types of OA of the knee are recognized: the more prevalent primary OA of the knee is considered to be a natural consequence of aging, whereas secondary OA of the knee can be caused by trauma, inactivity, overweight, or a disease process such as rheumatoid arthritis. No evidence suggests that the two types are treated differently or respond differently to treatments.<sup>1</sup>

In 2005, the estimated prevalence of osteoarthritis among adults in the United States (US), the number of individuals who had ever been told by a doctor that they had the condition, was approximately 27 million cases.<sup>2</sup> Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.<sup>3</sup> The prevalence of osteoarthritis of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for osteoarthritis of the knee are aging, obesity, prior injury, repetitive use,<sup>4</sup> and female gender. The US Centers for Disease Control have estimated that the prevalence of symptomatic knee osteoarthritis may reach 50 percent by the age of 85.<sup>5</sup> From 2002 to 2012, the number of individuals in the US with a total knee replacement (TKR) doubled from some 2 million to approximately 4 million.<sup>6</sup> The increase in obesity has translated not only into an increase in incidence of osteoarthritis of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with osteoarthritis of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,<sup>7</sup> and the risk that surgery will be needed has increased. Thus, the aging of the baby boomer population, along with the increased incidence and prevalence of obesity have increased the risk for this condition, all representing an increasing strain on Medicare resources.

**Diagnostic Strategies.** The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of OA may precede symptomatic OA but may not correlate with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence criteria. However, a number of versions of the criteria exist: At low cutoff scores, correlation with symptoms is poor,<sup>8</sup> whereas at higher cutoff scores, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies.<sup>8</sup> Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in

scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.<sup>9</sup> However, the sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and is not used in routine clinical practice.

***Treatment Strategies.*** The goals of treatment for osteoarthritis of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility, function (including activities of daily living [ADLs]), and health-related quality of life (HRQoL).

Treatment options for OA of the knee include analgesics (oral, intra-articular, or topical) and anti-inflammatory agents (non-steroidal anti-inflammatory agents [NSAIDs], intraarticular corticosteroids); dietary supplements (including glucosamine with or without chondroitin and herbal mixtures), variously proposed to control pain and possibly serve as disease modifying agents; Ayurvedic preparations, Traditional Chinese Medicine preparations, and acupuncture, all aimed at analgesia; physical treatments (including strength or aerobic exercise, physical therapy, stretching, heat, aqua-therapy, massage, and chiropractic manipulation), to strengthen muscles that support the affected joints and to increase range of motion; bracing or shoe inserts (orthoses), intended to slow progression by shifting the weight from the affected joint area; weight loss to decrease the stress on the joint; and if patients fail to obtain satisfactory relief from pain and improved function from the aforementioned treatments, arthroscopy with lavage and/or debridement, and partial or total arthroplasty (knee replacement) may be recommended for advanced cases. More recent therapies include intraarticular viscosupplementation, which involves local injections of the natural joint lubricant, hyaluronic acid (HA), experimental use of biologic agents (anti-nerve growth factor antibodies or anti-tumor necrosis factor antibodies, which are used to treat rheumatoid arthritis), as well as injections of platelet-rich plasma (PRP), plasma products, stem cells, and cartilage tissue, aimed at reversing or slowing the progression of the disease.<sup>10</sup> Information on the FDA status, indications, and warnings for the treatments included in this review is included in the Appendix.

Numerous recent evidence-based treatment guidelines have been issued, including the 2012 American College of Rheumatology Guidelines and<sup>10</sup> the 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee. These guidelines are not in total agreement about the recommended treatments: For example the 2012 American College of Rheumatology (ACR) Guidelines conditionally recommend HA, while the American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend against its use to treat patients with symptomatic conditions.<sup>11</sup>

***The Current Review*** Systematic reviews have been conducted on many of the modalities used to treat OA of the knee, including four reviews by AHRQ Evidence-based Practice Centers since

2007.<sup>1, 12, 13</sup> Uncertainty continues to surround the use of all treatments intended as disease-modifying agents (including HA and glucosamine and chondroitin), acupuncture, physical therapy, exercise, braces and orthotics, and arthroscopic lavage, as well as the comparative efficacy and safety of oral, topical, and intraarticular analgesics and anti-inflammatories.

The review that this protocol will guide is part of a continuous update review process that aims to repeatedly assess the need to update—and then to update if needed—a systematic review that was conducted in 2007<sup>1</sup> that assessed the efficacy and safety of HA, glucosamine and/or chondroitin, and arthroscopic surgery. Prior to preparing this protocol, we conducted an updating surveillance assessment that comprised an environmental scan and consultation with a technical expert panel (TEP) to assess the currency of the conclusions of the 2007 review.<sup>14</sup> A document that summarized the findings of this bifurcated process was posted for public review.<sup>15</sup> The treatment modalities selected for inclusion in the update review that this protocol will guide reflect a combination of the findings of the environmental scan, the TEP for the Surveillance process, the public comments, and the TEP.

The TEP for the surveillance process uniformly advised us that the conclusions of the 2007 report for intraarticular HA, oral glucosamine chondroitin, and arthroscopic surgery remained current and did not need updating. Instead, they recommended reviewing cell-based therapies, physical modalities, SNRIs, topical agents, weight loss, and acupuncture.

The environmental scan supported the TEP's suggestion that the topics of intra-articular HA and arthroscopic surgery did not need updating. However, we identified at least one large recent trial on glucosamine-chondroitin that prompted us to want to retain this topic in the update. Topics not included in this report will be re-assessed for the need to update in a later surveillance period.

The contributions of the public commenters are described further below, and the included topics (interventions) are listed in the PICOTs outline.

### **The Selection of Comparators for Intervention Trials**

One of the biggest challenges in conducting trials of the efficacy and safety of agents to control pain or improve function is the observed placebo effect and the need to identify appropriate placebo or sham controls. As a result of the divergent findings of several recent systematic reviews on the efficacy and safety of HA for OA of the knee, a commentary addressed the challenge of limiting risk of bias in such trials.<sup>16</sup> Inclusion of studies lacking placebo (saline) controls in systematic reviews of the efficacy of intraarticular HA has been shown to increase the pooled effect sizes for HA treatment significantly. In addition, two systematic reviews have focused on the effect of different placebos.<sup>17, 18</sup> To the extent possible, studies lacking appropriate placebo controls should be excluded from reviews of interventions with self-assessed pain, function, and quality of life as outcomes.

### **Assessment of Outcomes of Treatment**

Outcomes of treatment for OA of the knee include clinical outcomes and intermediate (physiological or structural) outcomes (such as joint space width). The latter will not be considered for the current review, as their applicability to patient-centered outcomes and clinical management has not been established.

A number of assessment tools are used to assess clinical outcomes of treatment such as pain, quality of life, and physical functioning in patients with osteoarthritis of the knee. These tools

can be divided into those specifically developed for knee osteoarthritis and those that are used for a variety of conditions.

Tools specifically developed and validated to assess pain and functioning associated with osteoarthritis of the knee as well as treatment outcomes include the Western Ontario-McMaster Universities Arthritis Index (WOMAC<sup>19</sup>), the Lequesne Index<sup>20</sup>, the Knee Injury and Osteoarthritis Outcomes Score (KOOS<sup>21</sup>), and the Animated Activity Questionnaire.<sup>22</sup> The Osteoarthritis Research Society International (OARSI) developed a consensus set of guidelines to assess the outcomes of research trials on products intended to treat osteoarthritis (the chair test, fast-paced walk test, stair climb test, timed up-and-go, and 6-minute walk test);<sup>23</sup> and under the International League of Rheumatologists, OMERACT (Outcome Measures in Rheumatology) has developed guidelines on outcome measures.<sup>24</sup>

General tools that have been adapted for use in assessing osteoarthritis of the knee include the Short form (SF)-36 (including the Physical Functioning Scale [PF-10]), developed at RAND for the Medical Outcomes Study;<sup>25</sup> the EuroQuol, EQ-5D™; and the Activities of Daily Living (ADLs) and IADLs assessment. The Kinemax Outcomes Group has used a combination of the WOMAC, the SF-36, and a series of questions addressing demographic characteristics to predict patient outcomes of total knee arthroplasty.<sup>26</sup> Newer tools include the Patient Reported Outcomes Measurement Information System (PROMIS)<sup>27</sup> for health-related quality of life and OA-Function-CAT (Computer Adaptive Test).<sup>28</sup>

Clinical significance must also be taken into consideration when interpreting the findings of individual clinical studies as well as pooled outcomes. Interventions may result in effect sizes that are statistically significant but not clinically meaningful to patients. Therefore, to the extent possible, pooled effect sizes need to be compared to minimum clinically important differences established for similar outcome measures and populations. A number of studies have addressed appropriate minimum clinically important differences (MCIDs) for treatments aimed at OA of the knee. In addition, the proportion of participants who experienced improvement should be abstracted if reported.

The systematic review, when complete, may serve to guide the formulation of future research questions and may be used to create or modify existing treatment guidelines.

## II. The Key Questions

### Introduction

Based on the findings of an initial surveillance process, described above, the key questions from the 2007 report were modified. These key questions were posted for public comment. Fifteen sets of comments were received in response to posting the proposed key questions. The following is a summary of the comments and any modifications we made to the key questions or PICOTs as a result of them.

*Populations.* No comments pertained to the populations. However, one commenter suggested trying to assess outcomes according to the localization of disease, e.g. medial vs. lateral and the patient's activity level as possible effect modifying factors. *Based on suggestions of the TEP and subject experts regarding the importance of assessing possible differences in response to treatment for participants with particular sites of OA involvement or differences in baseline*

*physical functioning, we will conduct subgroup analyses, if possible, on the effect of localization and baseline activity level on response to treatment.*

*Interventions.* Ten of the fifteen recommended inclusion of intra-articular hyaluronic acid treatment (a number of commenters were manufacturers or manufacturer representatives). *Because our EPC recently completed a SR on the effectiveness and safety of hyaluronic acid to treat OA of the knee, our environmental scan determined that no more recent original studies have been conducted, and both TEPs concurred, we made the decision not to include HA in the update review; however, we will reassess the need to update the review on HA when we update this report.*

Additional interventions recommended by the public commenters were combined pharmacological and non-pharmacological interventions, weight loss without physical activity, patient education and self-management, use of assistive devices, orthopedic braces, joint taping, and platelet rich plasma. *Based on these comments and those of the TEP and our environmental scan, we will include most of those suggested interventions in the review. However, assessment of the efficacy of combined interventions such as pharmacological and non-pharmacological interventions presents particular challenges that may necessitate our considering this topic at a later date.*

*Comparators.* No suggestions were made regarding comparators.

*Outcomes.* Additional *outcomes* were not suggested. However, one commenter suggested including only studies that reported patient specific outcomes. *Assuming this commenter meant individual patient data, the literature would not support following this suggestion; however, if, as several TEP members suggested, the commenter meant “patient-reported outcomes,” we will include only studies that report clinical outcomes, all of which have a component of patient reporting.*

*Timing.* No comments pertained to follow-up times but one suggested looking at the effects of weight loss and platelet rich plasma in early disease. *To the extent data are available to allow it, we will conduct subgroup analyses to assess early vs. late treatment effects.*

## **Revised Key Questions**

Based on the findings of the environmental scan, TEP assessments, and public comments, the key questions from the 2007 report were revised as follows.

1. a. What is the clinical effectiveness of oral glucosamine and/or chondroitin, physical treatments, weight loss, oral serotonin-norepinephrine reuptake inhibitors (SNRIs), intraarticular corticosteroids and/or prolotherapy, topical or transdermal analgesics, acupuncture, or cell-based therapies in patients with primary or secondary OA of the knee, compared with appropriate placebo/sham controls or compared with other active interventions?
- b. How do the outcomes of each intervention differ by the following population and study characteristics: sex, disease subtype (lateral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

2. a. What harms are associated with each intervention in patients with primary or secondary OA of the knee?

b. How do the harms associated with each intervention differ by the following population or study characteristics: sex, disease subtype (lateral tibiofemoral, patellofemoral), severity (stage/baseline pain and functional status), weight status (body mass index), baseline fitness (activity level), comorbidities, prior or concurrent treatments (including self-initiated therapies), and treatment duration or intensity?

## PICOTS

- Population(s) (for KQ1 and KQ2):
  - Adults (age 18 or over) with a diagnosis of primary (or secondary) OA of the knee, as defined by the American Academy of Orthopaedic Surgeons (AAOS, 2013), ACR clinical classification criteria,<sup>29</sup> or Kellgren-Lawrence stage.
  - Subpopulations of interest include those defined by sex, disease subtype (e.g., patellofemoral, or medial tibiofemoral), disease severity (stage/pain or functional status), body mass index, fitness/activity level, prior treatment, concurrent treatment(s), comorbidities
  - Exclusions:
    - Studies of individuals under age 18; those with OA caused by a congenital condition; and those with OA concomitant with a meniscal or anterior cruciate ligament tear will be excluded because these participants have conditions that differ importantly from the vast majority of OA patients
    - Studies that include those who have had knee replacement surgery on the affected limb or for whom outcomes will be measured after knee replacement surgery or who have concomitant joint disease such as rheumatoid arthritis or gout will be excluded because these conditions or procedures will confound assessment of the outcomes of interventions.
    - If three or more RCTs of a particular intervention are included that enroll at least 50 participants per study arm, smaller studies of the same intervention will be excluded unless they report on a subgroup analysis of interest because studies on management of OA of the knee that enroll fewer than 50 participants per study arm have been shown to have high risk of bias and significantly larger effect sizes.
- Interventions:
  - Pharmacologic treatments
    - Oral agents
      - Glucosamine and/or chondroitin
      - *SNRIs (to be assessed for review in next update)*
    - *Intra-articular injected agents (to be assessed for review in next update)*
      - *Corticosteroids (to be assessed for review in next update)*
      - *Prolotherapeutic agents (e.g. dextrose) (to be reviewed in next update)*
      - *Hyaluronic acid (to be assessed for review in next update)*
    - *Topical and transdermal agents (see Appendix table for brands) (to be*

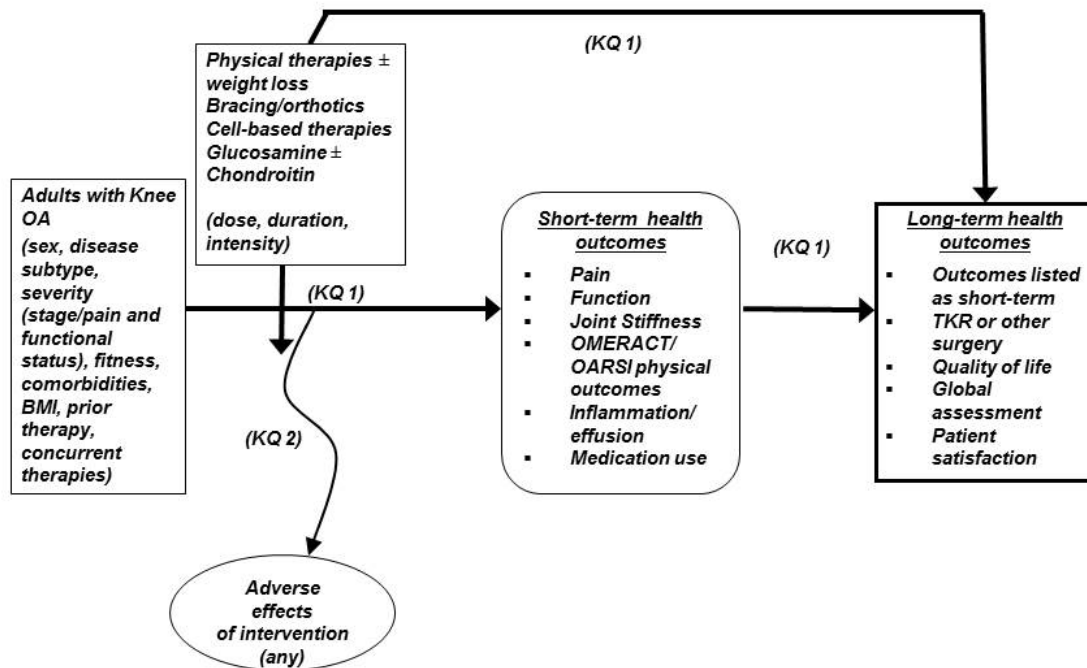
- assessed for review in next update)*
      - *Capsaicin (to be assessed for review in next update)*
      - *NSAIDs (to be assessed for review in next update)*
    - Cell-based therapies
      - Platelet-rich plasma
      - Intraarticular or arthroscopic administration of mesenchymal stem-cells or chondrocytes or tissue
      - Exclusions:
        - Phase I or II trials will not be included for efficacy, as the interventions are generally not FDA-approved for use.
    - Physical treatments and/or weight loss
      - Physical therapy and exercise programs
        - Manual therapy
        - Land-based therapy and/or exercise
        - Exercise programs (aerobic, resistance)
        - Aquatherapy,
        - Balneotherapy, mud therapy
        - Heat or cold
        - Self-management programs
      - Weight loss
      - Braces or kinesiology taping
      - Orthotic shoe inserts and/or wedges
      - Vibrating platform
      - Neuromuscular electrical stimulation (e.g., Transcutaneous electrical nerve stimulation)
    - *Acupuncture (to be assessed for review in next update)*
      - *Needle acupuncture alone (to be assessed for review in next update)*
      - *Moxibustion (to be assessed for review in next update)*
    - *Combination interventions (to be assessed for review in next update)*
      - *Sequential treatment algorithms (to be assessed for review in next update)*
  - Comparators:
    - Pharmacologic treatments: placebo-controlled or head-to-head non-inferiority only
    - Cell-based therapies: placebo- or sham-controlled only
    - Physical treatments and/or weight loss: placebo-controlled, usual care-controlled, or wait list-controlled only except for weight loss
    - Neuromuscular electrical stimulation: sham stimulation without current
    - Wait list
    - Treatment as usual
    - Studies that use the untreated knee as a control will be excluded, based on evidence indicating that individuals with OA in one knee are likely to have some, but not necessarily identically, reduced function in the other knee and that treatment of one knee only may improve pain in that knee but may not markedly improve function
    - Studies that use participants as their own controls will be excluded, unless no

randomized controlled trials are identified for a particular intervention of interest, as quasi-experimental designs provide weaker evidence.

- Exclusions:
  - Studies that use an active control that has not been established to be effective will be excluded. Efficacy and effectiveness must be established before examining comparative effectiveness questions.
- Outcomes:
  - Short-term clinical outcomes
    - Pain (e.g., VAS, WOMAC, KOOS,)
    - Joint stiffness (WOMAC)
    - Function (WOMAC, Lequesne, others)
    - OARSI physical outcomes (e.g., timed up-and-go, 6-minute walk test, )
    - Patient Reported Outcome Measurement System (PROMIS®) and Osteoarthritis-Computer Adaptive Test (OA-CAT)
    - Inflammation or effusion
    - Medication use
  - Long-term clinical outcomes
    - Any of the short-term clinical outcomes
    - Instrumental activities of daily living (IADLs)
    - Quality of life (e.g., SF-36, EuroQuol EQ-5D, Arthritis Self-Efficacy scale, global assessment, patient satisfaction)
    - Surgery (i.e., rate of undergoing knee replacement)
  - Adverse effects of intervention(s)
  - Outcome reporting
    - Only studies that report outcomes for knee OA alone
    - Mean differences at followup or percent of responders at followup will be abstracted
- Timing:
  - Minimum 1 month follow-up from initiation of treatment
- Settings:
  - Any setting

### III. Analytic Framework

Figure 1. Analytic Framework



#### IV. Methods

The methods that will be used to conduct the systematic review portion of this continuous update are based on the AHRQ Methods Guide.<sup>14</sup>

**Criteria for Inclusion/Exclusion of Studies in the Review** – The inclusion/exclusion criteria by target population, interventions, outcomes, comparators, setting, and study duration are shown in the PICOTs table. Study design and several additional criteria pertaining to the PICOTs are discussed here.

English language studies and those with an English–language abstract will be included, if resources are available for translation. We will exclude publications with both non-English abstracts and text, because of limited resources. Studies that test interventions that are not available in the US will also be excluded. As described in the PICOTs, if three or more RCTs are included for a particular intervention that enroll 50 participants or more per arm, we will consider excluding smaller studies of the same intervention unless the study reports a subgroup analysis of interest and is powered to conduct that analysis, based on repeated observations in prior systematic reviews of interventions for treatment of OA of the knee that inclusion of studies with sample sizes less than 50 per group significantly increased effect sizes and that such studies had higher risks of bias. Alternatively, we will include smaller studies and conduct sensitivity analyses to assess the effect of sample size.

Conference proceedings and letters that report sufficient information to enable assessment of risk of bias and that report unique data will be included.

We will limit included studies for assessment of efficacy to randomized controlled trials, with the exception of studies that assess the effects of weight loss. We will include prospective observational studies and case reports that report on adverse events associated with use of the interventions of interest for the treatment of OA of the knee.

With the exception of weight loss interventions, studies without controls and blinding will be excluded, based on the findings of prior reviews that the results of such studies can bias the results. For studies of physical therapies for which it is difficult to design a placebo control, such as exercise programs, braces, and orthoses, we will include studies with a treatment as usual or waiting list control group. Studies that compare an intervention of interest only to an intervention with no demonstrated evidence of efficacy (or unclear evidence of efficacy) will be excluded.

Studies will not be excluded simply because of low study quality (risk of bias) but if risk of bias varies in studies with positive results, we will conduct sensitivity analysis to assess the impact of elements of study quality.

The searches will commence with the year 2003, one year prior to the latest search dates of the original review we are updating. However, because we are also updating topics covered in EPC reviews conducted in 2012, we will not re-review studies included in (or actively excluded from) those reviews. Similarly, if we identify recent systematic reviews on other included topics (e.g., acupuncture) that match our review in key questions, outcomes of interest, and exclusion/inclusion criteria, we will weigh the feasibility of updating those reviews with any newer original studies rather than simply using those reviews as sources of references and conducting entirely new reviews (see Data Synthesis, below).

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions – Based on the methods used for the original report and recent reviews on similar topics, we will search the following databases for peer reviewed literature (dates discussed above): PubMed, EMBASE, the Cochrane Collection, and Web of Science. Based on pilot searches of these databases as well as the Physiotherapy Evidence Database (PEDRO), we will likely not include PEDRO search results. The proposed electronic search strategies were designed by the SCEPC reference librarian, who has over 15 years' experience designing and conducting literature searches for the EPC; the sample strategy for PubMed is shown in the Appendix.

The Web of Science and clinicaltrials.gov will be searched for as yet unpublished grey literature; and the abstracts from the past year of professional practice society annual meetings (e.g., American College of Rheumatology, American Academy of Orthopaedic Surgery) will be hand searched by members of the team with the appropriate clinical expertise. In addition, relevant stakeholders, including manufacturers of over-the-counter and prescription medications and medical devices used to treat OA of the knee will be contacted by the Scientific Resource Center for scientific information packets that contain any unpublished information on the efficacy and/or safety of their products when used specifically to treat OA of the knee; relevant information will be described narratively in the report. A notice will also be placed in the Federal Register requesting any relevant information on the use of dietary supplements containing glucosamine/chondroitin to treat OA of the knee. Titles identified by literature searches will be screened by pairs of experienced literature reviewers, without reconciliation of decisions. Abstracts of those titles selected for inclusion by one or both reviewers will be dually screened with disagreements reconciled by the project leaders, if necessary. Full text articles or other documents will be obtained for included abstracts. DistillerSR™ software will be used for screening, abstraction, reconciliation, and tracking. A 10-percent sample of titles for which no abstract can be identified will be obtained and reviewed in full-text to determine if we should obtain the full text publications for all titles of interest that lack an abstract. Such publications are typically commentaries, editorials, and letters to journal editors without original data.

Any references suggested by members of the TEP, peer reviewers, or public reviewers will be obtained and will undergo the same screening and abstraction process.

Data Abstraction and Data Management - Study-level details will be dually abstracted by the reviewers, using abstraction forms designed and piloted by the group (with at least two design iterations and some 10 to 25 articles per iteration, as suggested by the issues that are raised during piloting). Disagreements will be reconciled between reviewers with mediation by the project leaders if needed. Non-English articles will be obtained and abstracted only if a native speaker can easily be identified. Outcome data will be abstracted by an experienced biostatistical analyst and audited by an experienced reviewer. Risk of bias will be assessed by each reviewer, with disagreements reconciled. If primary outcome data appear to be lacking for a particular study or if peer reviewers note the existence of not-yet published data (particularly individual patient data), we will consider contacting study authors.

Studies that report outcomes in multiple publications will be noted, the publications mapped, and the records linked in Distiller to ensure consistency and avoid duplication of descriptions of study conditions. However, experience has shown that whereas some study level details remain the same across outcomes or subgroup analyses, the numbers and characteristics of participants

often differ, and risk of bias (ROB) sometimes differs across publications or analyses. Therefore, the information will be abstracted and ROB assessed by publication.

Study-level details to be collected, as noted in the PICOTs listed above, include participant age, sex, body mass index, diagnoses (stage, pain levels, functional status and activity level), comorbidities, and concurrent or prior treatments; numbers of participants enrolled and numbers who complete; inclusion/exclusion criteria; type and location of study site; number of sites; study and investigator funding; and potential conflicts of interest.

#### Assessment of Methodological Risk of Bias of Individual Studies

For randomized controlled trials of pharmacological interventions, glucosamine/chondroitin, and acupuncture, we will employ the Cochrane Risk of Bias Assessment tool to assess ROB of individual studies. Questions will be added to assess the type(s) of controls used and the way that outcomes are assessed (self-assessment, blinded assessor) and expressed (e.g., percent of participants who have a positive response, in addition to a weighted or standardized mean difference in response between treatment groups), as these factors have been shown to influence significance of effect sizes.

For trials of physical modalities, we will incorporate a small number of items from the PEDro risk of bias assessment tool. A recent analysis finds that the tools produce different assessments of the same studies, with the Cochrane tool providing a more rigorous assessment.<sup>30</sup>

For observational studies included to assess adverse events, we will use the McHarms scale for each study.

To assess the quality of prior systematic reviews that we include as sources of data, we will use the ROBIS tool.<sup>31</sup>

**Data Synthesis** – The evidence for both efficacy and safety will be presented together for each intervention. If studies are identified that compare different interventions head to head, we will discuss the results of these studies after describing the results of the placebo-controlled trials of individual interventions. For each intervention we propose to include, we will assess the most recent three years of published meta-analyses for their quality, the extent to which they match our key questions, PICOTs, other inclusion/exclusion criteria, and RoB and strength of evidence assessment criteria. If none are deemed sufficiently similar, we will use the existing meta-analyses as sources of original studies. However if we can identify a recent meta-analysis that matches our criteria and if we identify newer RCTs on the intervention, we will determine whether the newer studies can be added to the earlier meta-analyses, or more appropriately, whether new meta-analyses can be conducted, since the Hartung Knapp method for random effects meta-analysis is now favored. We will pool three or more studies we deem sufficiently similar in important participant characteristics (e.g., baseline disease severity), interventions, and followup times. If no new original studies are identified that can be pooled with earlier meta-analyses, we will describe the results of the earlier meta-analyses narratively. If new meta-analyses are done, these findings will be reported quantitatively with forest plots. If no new pooling is possible, we will describe the findings of newer studies qualitatively (narratively) by

the type of intervention. Studies of similar interventions will be grouped by outcome measures if feasible.

When pooling studies with continuous outcomes, to the extent possible, we will pool only studies with common measures to be able to compare with an MCID, where an MCID has been established. However, if most studies that report on a common outcome report different measures, we will conduct several different analyses as appropriate. We will calculate standardized mean differences across studies, pool those, and then conduct sensitivity analyses to assess the impact on the effect size of omitting studies that use less common outcome measures. If possible, we will also attempt to back-calculate effect sizes that represent common outcome measures.

If possible, subgroup analysis will be conducted to assess effects of disease severity, sex, comorbidities, baseline activity level, and adjunctive treatments on intervention outcomes. When appropriate to the intervention, we will explore the possibility of conducting meta-regressions to assess dose-response or differences within a particular class of intervention. Sensitivity analyses will be conducted for significant findings, using outliers, sample size, type of placebo/control, ROB (overall scores or specific concerns such as blinding or allocation concealment), and other selected factors such as average disease severity, age, or BMI of participants as the criteria. Adverse events identified in RCTs will be pooled if their numbers are reported separately by treatment group and if they are identified in such a way that they can be similarly categorized across studies. Adverse events reported in single arm trials and observational studies will be tabulated and reported separately.

### Grading the Strength of Evidence (SOE)

We will rate the strength of evidence (SoE) of each outcome based on the AHRQ Methods Guide. This review is intended to update a prior (2007) review in part. In addition, we will consider including the most recent systematic reviews/meta-analyses conducted for the other included interventions (including a 2012 EPC review on the use of physical modalities to treat pain from OA of the knee. If we determine that the findings of prior meta-analyses satisfy criteria for inclusion, we will reassess the RoB for a sample of studies included in the prior review and will review the SoE assessments for the conclusions.

Domains that will be used to assess SoE for conclusions based on pooled analyses will include study limitations (study design, ROB, overall methodological quality), consistency of the direction of effect sizes across studies, precision of the estimate (including number of studies), directness of the outcomes to the outcomes of interest, and magnitude of the effect size. Based on these domains, we will rate the SoE for each comparison of interest as high, moderate, low, or insufficient (if no or too few studies are identified that address the outcome). We will rate applicability of participant populations and interventions separately, as described below.

If prior meta-analyses are included as evidence in their entirety, their contribution to the overall SoE will depend on whether we include them in new meta-analyses (or simply report their pooled effect sizes). Based on our experience with other recent updates, we will most likely redo meta-analyses, combining previously included and new studies. If that is the case, studies included in the original review will be combined with newer studies to assess study limitations

and the remaining domains will be assessed according to the guidance provided by the GRADE Working Group.

If no new pooling is possible to address a particular outcome of interest, either because no new studies are identified, or new studies are too heterogeneous to pool, we will base conclusions on qualitative assessment of the individual studies. Prior meta-analyses will be treated as one study. Consistency will be assessed as the direction of the reported effect across studies, precision will be assessed in terms of the similarity in effect sizes, the average variance, and the numbers of studies. Directness will be assessed as it would for pooled outcomes.

Because we are including only trials for assessments of efficacy, the inclusion of observational studies will not contribute to assessments of overall SoE, although trial design will be considered as a study limitation. For assessments of safety, we will consider the consistency between the findings of trials to those of observational studies in assigning a SoE grade.

**Assessing Applicability** – We will consider applicability of participants and interventions separately from our assessment of directness for SoE. For assessing applicability of participant populations, studies that enroll younger age populations (mean age less than 50), those with only early stage or mild disease, those enrolling participants with mean BMI less than 25, or those with a higher activity level at baseline are likely to be considered less applicable.

For assessing applicability of interventions, studies of interventions with very high adherence (especially physical activity), studies that test custom off loader braces, and trials of moxibustion conducted in Asia will be considered somewhat less applicable than studies with lower adherence, off-the-shelf braces, and trials of moxibustion conducted in western countries (or trials of acupuncture alone). Stem cell therapy trials will not have high applicability as this treatment is currently limited in availability.

Follow-up times for studies of OA are nearly always too short for a chronic, progressive disease. Studies with shorter follow-up times (less than 3 months) will be considered to have lower applicability.

## V. References

## VI. Definition of Terms

Acronym/term/abbreviation	Definition
AAOS	American Academy of Orthopaedic Surgery
ACR	American College of Rheumatology
ADL	Activities of Daily Living
BMI	Body mass index
HRQoL	Health-related quality of life
IADL	Independent Activities of daily Living
NSAID	Non-steroidal anti-inflammatory drug
KOOS	Knee Injury and Osteoarthritis Outcome Score
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology and Clinical Trials
RCT	Randomized controlled trial
ROB	Risk of bias
SF-36	36-item Short Form (used to assess quality of life)
SoE	Strength of evidence

VAS	Visual assessment scale
WOMAC	Western Ontario McMaster Universities Arthritis Index

## VII. Summary of Protocol Amendments

## VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

## IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

#### XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

#### XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

#### XIII. Role of the Funder

This project was funded under Contract No. HHS A290201500010I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

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## Appendix A. Policies, Guidelines, Coverage, Stakeholder Information on Interventions of Interest

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage	Brand Names
Glucosamine Chondroitin	ACR: Conditional recommendation <i>against</i> use AAOS: Recommendation <i>against</i> use glucosamine and chondroitin (strong)	Evidence insufficient to demonstrate reduction in risk or disease modification (2004) Unclear regarding treatment of symptoms	Not relevant (over-the-counter)	
Platelet Rich Plasma	ACR: not mentioned AAOS: <i>unable</i> to recommend <i>for</i> or <i>against</i> growth factor injections and/or platelet rich plasma (inconclusive)	Off-label use for an FDA-approved product	CMS National Coverage Determination: covered only for certain chronic non-healing wounds	
Mesenchymal Stem Cells	ACR: not mentioned AAOS: not mentioned	Not approved by the FDA	Not covered for OA National Coverage Determination for Stem Cell Transplantation: <a href="https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&amp;ncdver=5&amp;NCAId=9&amp;IsPopup=y&amp;bc=AAAAAAAAAaAAAA%3D%3D&amp;">https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&amp;ncdver=5&amp;NCAId=9&amp;IsPopup=y&amp;bc=AAAAAAAAAaAAAA%3D%3D&amp;</a>	
Duloxetine	ACR: has no recommendation on using Duloxetine.  AAOS: not mentioned	Indicated for treatment of chronic musculoskeletal pain including discomfort from osteoarthritis and chronic lower back pain ( <a href="http://reference.medscape.com/drug/cymbalta-duloxetine-342960">http://reference.medscape.com/drug/cymbalta-duloxetine-342960</a> )	Not found (Medicare Part D coverage is plan dependent)	Effexor Eli Lilly and Co.
Herbal blends	ACR: not mentioned AAOS: not mentioned	Not relevant	Not relevant (over-the-counter)	
Topical or transdermal analgesics	ACR: conditionally recommends topical NSAIDs, topical capsaicin AAOS: not mentioned [unless the following → “We are unable to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee.” (inconclusive)]	FDA approval for OA in 1988. Black box warning regarding cardiovascular effects. Capsaicin patch is FDA-approved.	Not relevant for over-the-counter products; Coverage for prescription products is plan dependent.	Capzasin (Chattem, Inc.) Salonpas® methylsalicylate patch (Hisamatsu America, Inc.) Voltaren® Diclofenac transdermal patch (FLECTOR® IBSA Institut Biochimique SA, licensed by Alpharma Pharmaceuticals LLC, a subsidiary of Pfizer Inc)

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage	Brand Names
				Voltaren® Gel Diclofenac topical (Endo Pharmaceuticals, Inc. in collaboration with Sandoz, a subsidiary of Novartis)
Intraarticular corticosteroids	ACR: conditionally recommends intraarticular corticosteroid injections. AAOS: <i>unable to recommend for or against</i> the use of intraarticular (IA) corticosteroids (inconclusive)	Approved by the FDA for intralesional administration <a href="http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016466s040s041lbl.pdf">http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016466s040s041lbl.pdf</a>	Coverage is based on reasonable and necessary in addition to any other applicable regulation and guidance.	Aristospan (Sandoz, Inc.)  Depo-medrol (Pfizer/Pharmacia/Upjohn)
Intraarticular prolotherapy	Not addressed for knee OA	Injected dextrose is FDA-approved for treatment of hypoglycemia only	National noncoverage. <a href="https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&amp;ncdver=1&amp;bc=BAABAAA&amp;AAAA&amp;">https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&amp;ncdver=1&amp;bc=BAABAAA&amp;AAAA&amp;</a>	Abbot Labs manufactures dextrose for IV use
Acupuncture	ACR: conditionally recommends traditional Chinese acupuncture AAOS: cannot recommend using acupuncture in patients with symptomatic OAK (strong)	FDA approves acupuncture needles as medical devices <a href="https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=880.5580">https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=880.5580</a>	CMS National Coverage Determination (2004): not covered	
Weight loss	ACR: strongly recommends weight loss (for persons who are overweight) AAOS: suggests weight loss for patients with symptomatic osteoarthritis of the knee OAK and a BMI $\geq 25$ . (moderate)	Not searched	<b>Bariatric Surgery for the Treatment of Morbid Obesity</b> Certain procedures for the treatment of obesity are covered for Medicare beneficiaries who have a BMI $\geq 35$ , have at least one co-morbidity related to obesity and have been previously unsuccessful with the medical treatment of obesity. <a href="https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=57&amp;ncdver=5&amp;NCAId=258&amp;NcaName=Bariatric+Surgery+for+the+Treatment+of+Morbid+Obesity&amp;IsPopup=y&amp;bc=AAAAAAACAAAAA%3D%3D&amp;">https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=57&amp;ncdver=5&amp;NCAId=258&amp;NcaName=Bariatric+Surgery+for+the+Treatment+of+Morbid+Obesity&amp;IsPopup=y&amp;bc=AAAAAAACAAAAA%3D%3D&amp;</a>	Not relevant

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage	Brand Names
			<p><b>Other Treatments for Obesity</b></p> <p><b>Nationally Noncovered Indications</b></p> <p>1. Treatments for obesity alone remain non-covered.</p> <p>2. Supplemented fasting is not covered under the Medicare program as a general treatment for obesity, with certain exceptions.</p> <p>Where weight loss is necessary before surgery in order to ameliorate the complications posed by obesity when it coexists with pathological conditions such as cardiac and respiratory diseases, diabetes, or hypertension (and other more conservative techniques to achieve this end are not regarded as appropriate), supplemented fasting with adequate monitoring of the patient is eligible for coverage on a case-by-case basis or pursuant to a local coverage determination. The risks associated with the achievement of rapid weight loss must be carefully balanced against the risk posed by the condition requiring surgical treatment</p>	
Physical therapy	<p>ACR: conditionally recommends receiving manual therapy in combination with supervised exercise.</p> <p>AAOS: Not found specifically on physical therapy, although there were studies presented [unless if the following: "We are unable to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. (inconclusive)"]</p> <p>"We are unable to recommend for or against manual therapy in patients with symptomatic</p>	Not relevant	Covered under Part B subject to certain conditions and limitations	

Intervention	Current Guidelines	FDA Approval for Indicated Use	CMS Coverage	Brand Names
	osteoarthritis of the knee. (inconclusive)"]			
Braces and/or orthotics (orthoses or wedges)	ACR: conditionally recommends using medially directed patellar taping; wearing medially wedged insoles if a patient with OAK has lateral compartment OA, wearing laterally wedged subtalar strapped insoles if a patient with OAK have medial compartment OA; has no recommendations on wearing laterally wedged insoles and wearing knee braces. AAOS: cannot suggest that lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee. (moderate)	Unloader braces are approved by the FDA as medical equipment [need to check orthotics]	Medicare Part B covers medically necessary arm, leg, back, and neck braces under the durable medical equipment prefabricated <b>orthotics</b> benefit, subject to certain conditions and limitations. Shoes and foot orthotics are covered under certain circumstances only when criteria are met.	Ortho VQ and others

## **Appendix B. Search Methodology**

### **DATABASE SEARCHED & TIME PERIOD COVERED:**

PubMed – 1/1/2006-7/10/2015

### **LANGUAGE:**

English OR Non-English with English Abstract

### **SEARCH STRATEGIES:**

#### **GLUCOSAMINE:**

“osteoarthritis, knee”[MH] OR (“osteoarthritis”[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis\*[tiab] AND (knee[tiab] OR knees[tiab])) OR (“osteoarthritis”[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]) AND  
Glucosamine[MH] OR "Chondroitin"[MH] OR glucosamine OR acetylglucosamine OR  
"n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

#### **NEW THERAPIES:**

“osteoarthritis, knee”[MH] OR (“osteoarthritis”[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis\*[tiab] AND (knee[tiab] OR knees[tiab])) OR (“osteoarthritis”[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab]) AND  
monovisc OR duloxetine\* OR cymbalta OR selective serotonin\* OR ssri OR milnacipran OR savella OR  
venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin\* OR anakinra OR canakinumab OR  
"platelet rich plasma" OR "platelet-rich plasma" OR PRP OR "nerve growth factor" OR fibroblast growth OR shoe  
wedge\* OR capsaicin

### **MANUALLY SEARCHED ENDNOTE TO FILTER ABOVE RESULTS FOR THE FOLLOWING TERMS REPRESENTING STUDY DESIGNS:**

Comparative  
Evaluation  
Follow-up  
Follow up  
Prospective  
Placebo  
Clinical trial  
Mask  
Single-blind  
Double-blind  
Blind  
Random  
RCT  
Research design  
Control  
Volunteer  
Systematic review  
Meta-analy\*  
Meta analy\*  
Metaanaly\*  
Database or Data base  
Case series (for Arthroscopy only)

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### **DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase – 1/1/2006-7/21/2015

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)

Published online: June 15, 2016

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:****GLUCOSAMINE:**

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis'/exp OR osteoarthritis AND ('knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))

AND

'chondroitin' OR 'chondroitin'/exp OR chondroitin OR 'glucosamine' OR 'glucosamine'/exp OR glucosamine OR 'acetylglucosamine' OR 'acetylglucosamine'/exp OR acetylglucosamine OR 'n-acetylglucosamine'/exp OR 'n-acetylglucosamine' OR 'n-acetyl-d-glucosamine'/exp OR 'n-acetyl-d-glucosamine'

AND

Human/de

**NEW THERAPIES:**

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis'/exp OR osteoarthritis AND ('knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral'))

AND

'monovisc' OR 'monovisc'/exp OR monovisc OR duloxetine\* OR 'cymbalta' OR 'cymbalta'/exp OR cymbalta OR (selective AND serotonin\*) OR 'ssnri' OR 'ssnri'/exp OR ssnri OR 'milnacipran' OR 'milnacipran'/exp OR milnacipran OR 'savella' OR 'savella'/exp OR savella OR 'venlafaxine' OR 'venlafaxine'/exp OR venlafaxine OR 'effexor' OR 'effexor'/exp OR effexor OR 'desvenlafaxine' OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'pristiq' OR 'pristiq'/exp OR pristiq OR 'il-1'/exp OR 'il-1' OR interleukin\* OR 'anakinra' OR 'anakinra'/exp OR anakinra OR 'canakinumab' OR 'canakinumab'/exp OR canakinumab OR 'platelet rich plasma'/exp OR 'platelet rich plasma' OR 'platelet-rich plasma'/exp OR 'platelet-rich plasma' OR 'prp' OR 'prp'/exp OR prp OR 'nerve growth factor'/exp OR 'nerve growth factor' OR (('fibroblast' OR 'fibroblast'/exp OR fibroblast) AND ('growth' OR 'growth'/exp OR growth)) OR (('shoe' OR 'shoe'/exp OR shoe) AND wedge\*) OR capsaicin\*

AND

Human/de

**MANUALLY SEARCHED ENDNOTE TO FILTER ABOVE RESULTS FOR THE FOLLOWING TERMS REPRESENTING STUDY DESIGNS:**

Comparative

Follow-up

Follow up

Prospective

Placebo

Trial

Mask

Single-blind

Double-blind

Blind

Random

RCT

Research design

Control

Volunteer

Systematic review

Meta-analy\*

Meta analy\*

Database or Data base

Case series (for Arthroscopy only)

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

Cochrane Databases of Systematic Reviews, Other Reviews, CENTRAL, Methods, Technology Assessment, Economic Evaluations – 1/1/2006-8/3/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:****GLUCOSAMINE:**

osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw

AND

glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin:ti,ab,kw

**NEW THERAPIES:**

osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw

AND

monovisc or duloxetine\* or cymbalta or selective serotonin\* or ssni or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin:ti,ab,kw

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

International Pharmaceutical Abstracts – 1/1/2006-8/4/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:****GLUCOSAMINE:**

ab(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR ti(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR su(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))

AND

ab(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR ti(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin) OR su(glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin)

**NEW THERAPIES:**

ab(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR ti(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)) OR su(osteoarthritis and (knee or knees or patellofemoral or patello-femoral))

AND

ab(monovisc or duloxetine\* or cymbalta or selective serotonin\* or ssni or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin) OR ti(monovisc or duloxetine\* or cymbalta or selective serotonin\* or ssni or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin) OR su(monovisc or duloxetine\* or cymbalta or selective serotonin\* or ssni or milnacipran or savella or venlafaxine or

effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin)

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## UPDATES RUN IN NOVEMBER/DECEMBER 2015

### DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed – 6/1/2015-11/4/2015

### LANGUAGE:

English OR Non-English with English Abstract

### SEARCH STRATEGIES:

#### GLUCOSAMINE:

"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis\*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab])) AND

Glucosamine[MH] OR "Chondroitin"[MH] OR glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

#### NEW THERAPIES:

### DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed – 6/1/2015-12/2/2015

"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis\*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab])) AND

duloxetine\* OR cymbalta OR selective serotonin\* OR ssni OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin\* OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR PRP OR "nerve growth factor" OR fibroblast growth OR shoe wedge\* OR capsaicin

### ADDITIONAL THERAPIES:

### DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed - 1/1/2006-12/11/2015

### LANGUAGE:

English OR Non-English with English Abstract

### SEARCH STRATEGIES:

"osteoarthritis, knee"[MH] OR ("osteoarthritis"[MH] AND (knee[tiab] OR knees[tiab])) OR (osteoarthritis\*[tiab] AND (knee[tiab] OR knees[tiab])) OR ("osteoarthritis"[MH] AND (patellofemoral[tiab] OR patello-femoral[tiab])) OR ("osteoarthritis"[tiab] AND (patellofemoral[tiab] OR patello-femoral[tiab])) AND

acupuncture[tiab] OR acupuncture[ot] OR braces OR orthotic\* OR orthosis OR orthoses OR stem cell\* OR physical therapy OR exercis\* OR herbal supplement\* OR transdermal OR topical analgesic\* OR analgesic cream\* OR prolotherap\* OR weight loss OR losing weight OR diet OR dieting OR weight reduc\* OR cell-based therap\* OR "Acupuncture Therapy"[Mesh] OR "Orthotic Devices"[Mesh] OR "Stem Cells"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Exercise Therapy"[Mesh] OR "Transdermal Patch"[Mesh] OR "Weight Loss"[Mesh] OR "Diet, Reducing"[Mesh] OR "Weight Reduction Programs"[Mesh] OR (dietary supplements[mh] AND (plants, medicinal[mh] OR plant extracts[mh])) OR (administration, topical[mh] AND analgesics[mh])

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase – 1/1/2015-11/5/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:****GLUCOSAMINE:**

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral')) AND [english]/lim AND [humans]/lim AND [2015-2015]/py  
AND  
'chondroitin' OR 'chondroitin'/exp OR chondroitin OR 'glucosamine' OR 'glucosamine'/exp OR glucosamine OR 'acetylglucosamine' OR 'acetylglucosamine'/exp OR acetylglucosamine OR 'n-acetylglucosamine'/exp OR 'n-acetylglucosamine' OR 'n-acetyl-d-glucosamine'/exp OR 'n-acetyl-d-glucosamine'

**NEW THERAPIES:****DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase – 1/1/2015-11/5/2015

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR ('osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral')) AND  
duloxetine\* OR 'cymbalta' OR 'cymbalta'/exp OR cymbalta OR (selective AND serotonin\*) OR 'ssnri' OR 'ssnri'/exp OR ssnri OR 'milnacipran' OR 'milnacipran'/exp OR milnacipran OR 'savella' OR 'savella'/exp OR savella OR 'venlafaxine' OR 'venlafaxine'/exp OR venlafaxine OR 'effexor' OR 'effexor'/exp OR effexor OR 'desvenlafaxine' OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'pristiq' OR 'pristiq'/exp OR pristiq OR 'il-1'/exp OR 'il-1' OR interleukin\* OR 'anakinra' OR 'anakinra'/exp OR anakinra OR 'canakinumab' OR 'canakinumab'/exp OR canakinumab OR 'platelet rich plasma'/exp OR 'platelet rich plasma' OR 'platelet-rich plasma'/exp OR 'platelet-rich plasma' OR 'prp' OR 'prp'/exp OR prp OR 'nerve growth factor'/exp OR 'nerve growth factor' OR ('fibroblast' OR 'fibroblast'/exp OR fibroblast AND ('growth' OR 'growth'/exp OR growth)) OR ('shoe' OR 'shoe'/exp OR shoe AND wedge\*) OR capsaicin\*  
AND  
Human

**ADDITIONAL THERAPIES:****DATABASE SEARCHED & TIME PERIOD COVERED:**

Embase - 1/1/2006-12/11/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

'knee osteoarthritis'/exp OR 'knee osteoarthritis' OR 'osteoarthritis' OR 'osteoarthritis'/exp OR osteoarthritis AND ('knee' OR 'knee'/exp OR knee OR knees OR patellofemoral OR 'patello femoral')  
AND  
'acupuncture' OR 'acupuncture'/exp OR acupuncture OR 'braces' OR 'braces'/exp OR braces OR orthotic\* OR 'orthosis' OR 'orthosis'/exp OR orthosis OR 'orthoses' OR 'orthoses'/exp OR orthoses OR (stem AND cell\*) OR (physical AND ('therapy' OR 'therapy'/exp OR therapy)) OR exercis\* OR herbal AND supplement\* OR 'transdermal' OR 'transdermal'/exp OR transdermal OR ('topical' OR 'topical'/exp OR topical AND analgesic\*) OR ('analgesic' OR 'analgesic'/exp OR analgesic AND cream\*) OR prolotherap\* OR ('weight' OR 'weight'/exp OR

weight AND (loss OR losing) OR 'diet' OR 'diet'/exp OR diet OR 'dieting' OR 'dieting'/exp OR dieting OR ('weight' OR 'weight'/exp OR weight AND reduc\*) OR '(cell based' AND therap\*)  
AND  
Humans

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

Cochrane – 1/1/2015-11/5/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

**GLUCOSAMINE:**

osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw (Word variations have been searched)

AND

glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin:ti,ab,kw (Word variations have been searched)

**NEW THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Cochrane – 1/1/2015-12/2/2015

**SEARCH STRATEGY:**

osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw Publication Year from 2015 to 2015 (Word variations have been searched)

AND

duloxetine\* or cymbalta or selective serotonin\* or ssni or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin:ti,ab,kw (Word variations have been searched)

**ADDITIONAL THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Cochrane - 1/1/2006-12/11/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

osteoarthritis and (knee or knees or patellofemoral or patello-femoral):ti,ab,kw (Word variations have been searched)

AND

acupuncture or braces or orthotic\* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis\* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap\* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies" 143386

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

CINAHL – 1/1/2006-11/12/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

**GLUCOSAMINE:**

TI ( osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) ) OR AB ( osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) ) OR SU ( osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) )

AND

TI ( glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin ) OR AB ( glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin ) OR SU ( glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin )

**NEW THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

CINAHL – 1/1/2006-12/2/2015

**SEARCH STRATEGY:**

TI ( osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) ) OR AB ( osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) ) OR SU ( osteoarthritis AND (knee or knees or patellofemoral or patello-femoral) )

AND

TI ( duloxetine\* or cymbalta or selective serotonin\* or ssri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin ) OR AB ( duloxetine\* or cymbalta or selective serotonin\* or ssri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin ) OR SU ( duloxetine\* or cymbalta or selective serotonin\* or ssri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin )

**ADDITIONAL THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

CINAHL - 1/1/2006-12/4/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

TI ( osteoarthritis and (knee or knees or patellofemoral or patello-femoral) ) OR AB ( osteoarthritis and (knee or knees or patellofemoral or patello-femoral) ) OR SU ( osteoarthritis and (knee or knees or patellofemoral or patello-femoral) )

AND

TI ( acupuncture or braces or orthotic\* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis\* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap\* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies" ) OR AB ( acupuncture or braces or orthotic\* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis\* or "herbal supplement" or "herbal supplements" or transdermal or

"topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap\* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies" ) OR SU ( acupuncture or braces or orthotic\* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis\* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap\* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies")

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

Web of Science – Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC 1/1/2006-12/2/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

**GLUCOSAMINE:**

TOPIC: (osteoarthritis and (knee or knees or patellofemoral or patello-femoral)

AND

TOPIC: (glucosamine or acetylglucosamine or "n-acetylglucosamine" or "n-acetyl-d-glucosamine" or chondroitin)

**NEW THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Web of Science – Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC 1/1/2006-12/2/2015

**SEARCH STRATEGY:**

TS=(osteoarthritis and (knee or knees or patellofemoral or patello-femoral)

AND

TS=(duloxetine\* or cymbalta or selective serotonin\* or ssni or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin)

**ADDITIONAL THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Web of Science Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC - 1/1/2006-12/14/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

ts=(osteoarthritis) AND ts=(knee or knees or patellofemoral or patello-femoral)

AND

ts=(acupuncture or braces or orthotic\* or orthosis or orthoses or "stem cell" or "stem cells" or "physical therapy" or exercis\* or "herbal supplement" or "herbal supplements" or transdermal or "topical analgesic" or "topical analgesics" or "analgesic cream" or "analgesic creams" or prolotherap\* or weight or diet or dieting or "cell-based therapy" or "cell-based therapies")

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

Scopus - 1/1/2006-11/6/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

**GLUCOSAMINE:**

TITLE-ABS-KEY ( osteoarthritis AND ( knee OR knees OR patellofemoral OR patello-femoral ) ) AND

TITLE-ABS-KEY ( glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin ) )

AND

SUBJAREA ( mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci )

**NEW THERAPIES**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

Scopus - 1/1/2006-12/2/2015

**SEARCH STRATEGY:**

TITLE-ABS-KEY ( osteoarthritis AND ( knee OR knees OR patellofemoral OR patello-femoral ) ) AND SUBJAREA ( mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci )

AND

TITLE-ABS-KEY ( duloxetine\* OR cymbalta OR selective serotonin\* OR ssnri OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristi OR "il-1" OR interleukin\* OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR prp OR ( "nerve growth factor" OR fibroblast growth OR shoe wedge\* OR capsaicin )

AND

SUBJAREA ( mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci )

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

International Pharmaceutical Abstracts - 6/29/2015-11/18/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGY:**

ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

AMED (Allied & Complementary Medicine) - 6/29/2015-11/18/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

**GLUCOSAMINE:**

ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))

AND

ab(glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin) OR ti(glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin) OR su(glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin)

**NEW THERAPIES:****DATABASE SEARCHED & TIME PERIOD COVERED:**

AMED (Allied & Complementary Medicine) - 6/29/2015-11/18/2015

**SEARCH STRATEGY:**

ab(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR ti(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral)) OR su(osteoarthritis AND (knee OR knees OR patellofemoral OR patello-femoral))

AND

ab(duloxetine\* or cymbalta or selective serotonin\* or ssri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin) OR ti(duloxetine\* or cymbalta or selective serotonin\* or ssri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin) OR su(duloxetine\* or cymbalta or selective serotonin\* or ssri or milnacipran or savella or venlafaxine or effexor or desvenlafaxine or pristiq or "il-1" or interleukin\* or anakinra or canakinumab or "platelet rich plasma" or "platelet-rich plasma" or PRP or "nerve growth factor" or fibroblast growth or shoe wedge\* or capsaicin)

**DATABASE SEARCHED & TIME PERIOD COVERED:**

ClinicalTrials.gov – 1/1/2006-11/10/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:****GLUCOSAMINE:**

KEYWORD :knee OR knees OR patellofemoral OR patello-femoral

AND

CONDITION:osteoarthritis

AND

INTERVENTION: glucosamine OR acetylglucosamine OR "n-acetylglucosamine" OR "n-acetyl-d-glucosamine" OR chondroitin

**NEW THERAPIES:**

KEYWORD:knee OR knees OR patellofemoral OR patello-femoral

AND

CONDITION:osteoarthritis

AND

INTERVENTION: duloxetine OR cymbalta OR selective serotonin OR ssri OR milnacipran OR savella OR venlafaxine OR effexor OR desvenlafaxine OR pristiq OR "il-1" OR interleukin OR anakinra OR canakinumab OR "platelet rich plasma" OR "platelet-rich plasma" OR PRP OR "nerve growth factor" OR fibroblast growth OR shoe wedge OR shoe wedges OR capsaicin

**ADDITIONAL THERAPIES:**

**DATABASE SEARCHED & TIME PERIOD COVERED:**

ClinicalTrials.gov - 1/1/2006-12/21/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

KEYWORD: knee OR knees OR patellofemoral OR patello-femoral

CONDITION: osteoarthritis

INTERVENTION: acupuncture OR stem cell OR stem cells OR physical therapy OR diet OR diets OR nutrition OR nutritional OR weight OR obese OR obesity OR dietary supplements OR transdermal OR patch OR plant OR plants OR exercise OR exercising OR topical analgesic OR topical analgesics OR analgesic cream OR analgesic creams OR brace OR braces OR orthotic OR orthotics OR orthosis OR orthoses OR herbal supplement OR herbal supplements OR prolotherapy or prolotherapies OR prolotherapeutic OR cell-based

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

PEDRO - 1/1/2006-12/11/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGIES:**

Abstract & Title: Osteoarthritis

AND

Abstract & Title: knee

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**DATABASE SEARCHED & TIME PERIOD COVERED:**

WHO International Clinical Trials Registry - 1/1/2006-12/15/2015

**LANGUAGE:**

English OR Non-English with English Abstract

**SEARCH STRATEGY:**

CONDITION: Osteoarthritis AND knee